Emerging Infections Program (EIP) Network Report Healthcare-Associated Infections Community Interface Multi-site Gram-negative Surveillance Initiative Carbapenem-Resistant Enterobacteriaceae (CRE) Surveillance, 2015

EIP Areas
Colorado (5 county Denver area); Georgia (8 county Atlanta area); Maryland (4 county Baltimore area); Minnesota (2 county Minneapolis – St. Paul area); New Mexico (1 county Albuquerque area); New York (1 county Rochester area); Oregon (3 county Portland area); and Tennessee (8 county Nashville area).

Population
The surveillance areas represent 15,226,087 persons.
Source: National Center for Health Statistics bridged-race vintage 2015 postcensal file.

Case Definition
A CRE case was defined as isolation of *Escherichia coli*, *Enterobacter aerogenes* (now *Klebsiella aerogenes*), *Enterobacter cloacae* complex, *Klebsiella pneumoniae,* or *Klebsiella oxytoca* with the following criteria:

- Carbapenem-nonsusceptible (doripenem, imipenem, or meropenem) and resistant to all tested third generation cephalosporins (ceftriaxone, ceftazidime, or cefotaxime) using the 2015 Clinical and Laboratory Standards Institute clinical breakpoints (1);
- Isolated from either a normally sterile body site (e.g., blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body sites, or muscle) or urine;
- Identified in residents of the surveillance area in 2015.

Because the clinical breakpoint defining resistance to ertapenem in Enterobacteriaceae is lower than the clinical breakpoint for other carbapenems, ertapenem was excluded from this CRE definition to increase specificity for carbapenemase-producing CRE.

Methodology
Case finding was active, laboratory-based, and population-based. Clinical laboratories that serve residents of the surveillance area were routinely contacted for case identification through a query of minimum inhibitory concentration (MIC) values from automated testing instruments. When possible, the MIC values obtained directly from the automated testing instruments were used to determine if an isolate met the phenotypic case definition. An incident CRE case was defined as the first CRE isolate meeting the case definition from a patient during a 30-day period.

A standardized case report form was completed for each incident case through review of medical records. Inpatient and outpatient medical records were reviewed for information on patient demographics, clinical syndrome, outcome of illness, and relevant healthcare exposures.

A convenience sample of CRE isolates (N=227) was collected from EIP sites and submitted to CDC for additional testing including species confirmatory testing, antimicrobial susceptibility testing by reference broth microdilution with a metallo-β-lactamase (MBL) screen, screening for carbapenemase production using the Modified Hodge Test (MHT), polymerase chain reaction (PCR) screening for KPC, NDM, and OXA-48-like carbapenemase genes, and PCR testing for other carbapenemase genes (i.e., VIM) if MBL screen positive and negative for KPC, NDM, and OXA-48-like genes.

Incidence rates for CRE cases were calculated using the 2015 US Census estimates of the surveillance area population as the denominator.

Assessment of vital status in patients admitted to a hospital occurred at the time of discharge from the acute care hospital. For patients in a long-term care facility, long-term acute care facility, or in an outpatient dialysis center, vital status was assessed 30 days after culture collection. For all other patients, vital status was assessed using medical records from the healthcare facility encounter associated with the culture.

CRE surveillance data underwent regular data cleaning to ensure accuracy and completeness. Patients with complete case report form data as of 1/2/2020 were included in this analysis. Because data can be updated as needed, analyses of datasets generated on a different date may yield slightly different results.

Results

Table 1. Specimen Sources for Incident CRE Cases by Organism (N=451), 2015

CRE Organism	Total	Urine No.	Urine %	Blood[a] No.	Blood %	Other Sterile Sites No.	Other Sterile Sites %
Enterobacter Klebsiella aerogenes	57	52	91.2	4	7.0	1	1.8
Enterobacter cloacae complex	75	66	88.0	6	8.0	3	4.0
Escherichia coli	88	80	90.9	7	8.0	1	1.1
Klebsiella pneumoniae	224	188	83.9	35	15.6	1	0.4
Klebsiella oxytoca	7	6	85.7	1	14.3	0	0
Total	451	392	86.9	53	11.8	6	1.3

[a] Category includes cases with both a positive blood and urine specimen collected.

Table 2a. Molecular Characteristics of CRE Isolates Submitted to CDC Based on Testing Performed at CDC (N=227), 2015

Organism	Isolates Submitted to CDC	Carbapenemase-Producing No.[a, b]	%
Enterobacter (*Klebsiella*) *aerogenes*	30	0	0
Enterobacter cloacae complex	49	12/49	24.5
Escherichia coli	39	11/39	28.2
Klebsiella pneumoniae	107	86/107	80.4
Klebsiella oxytoca	2	0	0
Total	227	109/227	48.0

[a]Testing was performed by PCR.

[b]Carbapenemase-producing isolates were collected from urine (n=93/109; 85.3%), blood (n=15/109; 13.8%), and other sterile sites (n=1/109; 0.9%).

Table 2b. Molecular Characteristics of CRE Isolates Submitted to CDC Based on Testing Performed at CDC (N=227), 2015 by Carbapenemase Gene

Organism	KPC No.	KPC %	NDM No.	NDM %	OXA-48-like No.	OXA-48-like %
Enterobacter (*Klebsiella*) *aerogenes*	0	0	0	0	0	0
Enterobacter cloacae complex	12	24.5	0	0	0	0
Escherichia coli	9	23.1	2	5.1	0	0
Klebsiella pneumoniae	85	79.4	1	0.9	0	0
Klebsiella oxytoca	0	0	0	0	0	0
Total	106	46.7	3	1.3	0	0

Table 2c. Confirmatory Antimicrobial Susceptibility Results of CRE Isolates Submitted to CDC

Organism	Carbapenem-resistant No.[c]	Carbapenem-resistant %[c]	Difficult to Treat No.[d]	Difficult to Treat %
Enterobacter (*Klebsiella*) *aerogenes*	7	23.3	0	0
Enterobacter cloacae complex	32	65.3	7	14.3
Escherichia coli	17	43.6	5	12.8
Klebsiella pneumoniae	94	87.9	73	68.2
Klebsiella oxytoca	1	50.0	1	50.0
Total	151	66.5	86	37.9

[c]Carbapenem resistance is defined as resistance to doripenem, ertapenem, imipenem, or meropenem, which differs from the surveillance case definition.

[d]Difficult to treat is defined as non-susceptibility to all first-line agents tested (i.e., carbapenems, extended-spectrum cephalosporins, fluoroquinolones, piperacillin-tazobactam, and aztreonam) (2).

Table 3. Incidence Rates for CRE Cases by Sex, Race, and Age (N=451), 2015

Sex	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
Female	268	3.44	3.41, 3.46
Male	183	2.46	2.44, 2.49

Race	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
White	213	1.99	1.97, 2.01
Black or African American	174	5.22	5.16, 5.28
Other[a]	18	1.51	1.35, 1.68
Unknown	46	N/A	N/A

Age group, years	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
0–18	11	0.29	0.25, 0.35
19–49	73	1.09	1.06, 1.12
50–64	127	4.37	4.30, 4.44
65–79	152	10.62	10.48, 10.75
≥80	88	19.24	18.81, 19.67
Invasive cases[b]	65	0.43	0.41, 0.44
All cases	451	2.96	2.95, 2.97

[a]Other race includes Asian and American Indian or Alaska Native.

[b]Invasive cases include cases with a sterile incident specimen source or an incident urine specimen with a subsequent non-incident sterile specimen collected on the date of incident specimen collection or in the 29 days after.

Table 4. Clinical Characteristics and Infection Types for Incident CRE Cases (N=451), 2015[a]

No. of Immunocompromised[b] Cases	%
39	8.6

Infection types	No. of Cases	%
Urinary tract infection[c]	299	66.3
Bacteremia[d]	63	14.0
Septic shock	25	5.5
Pneumonia	6	1.3
Other infection types	16	3.5
None[e]	72	16.0
Unknown	26	5.8

[a]Patients could have more than one type of infection reported.
[b]Immunocompromised includes solid organ transplant recipients and patients with a documented diagnosis of AIDS or a hematologic malignancy.
[c]Among 299 cases with a documented urinary tract infection (UTI), 138 (46.2%) had signs and symptoms associated with a UTI documented in the medical record. Reported signs and symptoms included fever, dysuria, frequency, urgency, costovertebral angle pain or tenderness, and suprapubic tenderness.
[d]Bacteremia includes cases with a positive blood specimen (incident or non-incident) or a documented diagnosis of sepsis, septicemia, bacteremia, or blood stream infection.
[e]No infection types reported.

Table 5. Patient Location Before, During, and After Incident Specimen Collection Among Incident CRE Cases (N=451), 2015

Residence before incident specimen collection	No. of Cases	%
Private residence or Homeless	182	40.4
Long-term care facility	160	35.5
Acute care hospital inpatient	79	17.5
Long-term acute care hospital	22	4.9
Unknown	8	1.8

Collection location	No. of Cases	%
Outpatient setting or emergency department	213	47.2
Acute care hospital	128	28.4
Long-term care facility	90	20.0
Long-term acute care hospital	16	3.5
Unknown	4	0.9

Hospitalized on the day of or in the 29 days after the date of incident specimen collection	No. of Cases	%
Hospitalized	252	55.9
Not hospitalized	190	42.1
Unknown	9	2.0

Discharge location among hospitalized patients (N=252)	No. of Cases	%
Long-term care facility	122	48.4
Private residence	90	35.7
Long-term acute care hospital	15	6.0
Died during hospitalization	24	9.5
Unknown	1	0.4

Table 6. Outcome of CRE Cases (N=451), 2015

Outcome	No. of Cases	%
ICU admission in the 6 days after the date of incident specimen collection	60	13.3
Died	29	6.4
Cases with a positive incident sterile site specimen (N=59)	13	22.0
Cases with a positive incident urine specimen (N=392)	16[a]	4.1

[a]None had a subsequent non-incident blood specimen collected on the date of incident specimen collection or in the 29 days after.

Table 7. Selected Characteristics of Incident CRE Cases (N=451), 2015[a]

Exposure	No. of Cases	%
Healthcare facility stay in the year before the date of incident specimen collection	343	76.1
Acute care hospital	298	66.1
Long-term care facility	219	48.6
Long-term acute care hospital	55	12.2
Surgery in the year before the date of incident specimen collection	129	28.6
In ICU in the 7 days before the date of incident specimen collection	47	10.4
Specimen collected ≥3 days after hospital admission	79	17.5
Chronic dialysis	24	5.3
Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection	267	59.2
Urinary catheter	191	42.4
Central venous catheter	123	27.3
Other[b]	150	33.3
None of the above healthcare exposures[c]	52	11.5
International travel in the 2 weeks before the date of incident specimen collection	5	1.1

[a]Patients could have more than one prior healthcare risk factor reported.
[b]Other medical devices include: endotracheal or nasotracheal tube, tracheostomy, gastrostomy tube, nephrostomy tube, nasogastric tube.
[c]Defined as having no healthcare exposures in the year before specimen collection, no selected medical devices in place in the 2 days before specimen collection, and specimen collected before calendar day 3 after hospital admission if hospitalized.

Summary

The overall crude incidence rate of CRE in 2015 was 2.96 cases per 100,000 persons and was lower than the incidence rate in 2014 (3.52 cases per 100,000 persons). The incidence rate increased with age, was higher in women than in men, and higher in persons of Black or African American race than in persons of other races. Most CRE were isolated from a urine source rather than from normally sterile body sites. Prior healthcare exposures were reported for most cases, with hospitalization in the prior year, presence of indwelling medical devices, and prior long-term care facility residency being the most common exposures. More than half of the cases required hospitalization, and overall crude mortality rate was 6.4%, with a higher mortality observed in cases with a sterile-site specimen source compared to those with a urine specimen source.

Among the 227 isolates submitted to CDC, 48% were carbapenemase-producing. KPC was all but three carbapenemase-producing isolates, and NDM was detected in these three isolates.

References

1. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement*. CLSI document M100-S25 (ISBN 1-56238-990-4). Wayne, PA 2015.
2. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis. 2018 Nov 28;67(12):1803-14.

Citation

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